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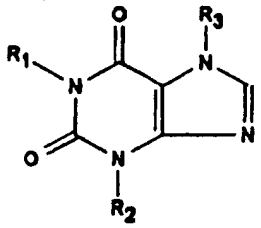
(54) Title: TOPICAL GEL COMPOSITION CONTAINING A COMBINATION OF A NSAID AND A XANTHINE DERIVATIVE

(57) Abstract

Topical gel composition comprising: (a) from about 0.1 % to about 10 % by weight of a non-steroidal anti-inflammatory drug selected from a propionic acid derivative, acetic acid derivative, fenamic acid derivative, biphenylcarboxylic acid derivative and an oxicam, and salts thereof, and mixtures thereof; (b) from about 0.1 % to about 10 % by weight of xanthine derivative having general formula (I), wherein R1, R2 and R3 are each independently selected from a hydrogen atom, a methyl or ethyl group, and at least two of R1, R2 and R3 are methyl or ethyl groups, or mixtures thereof: (c) from about 0.5 % to about 10 % by weight of gelling agent; (d) from about 5 % to about 60 % by weight of cosolvent for said non-steroidal anti-inflammatory drug and said xanthine derivative; (e) from about 10 % to about 90 % by weight of water. The compositions of the invention provide enhanced product stability and clarity and analgesic and anti-inflammatory activity.



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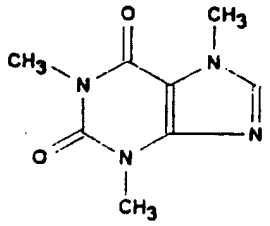
TOPICAL GEL COMPOSITION CONTAINING A COMBINATION OF A NSAID AND A XANTHINE DERIVATIVE

Field of the Invention

The present invention relates to pharmaceutical compositions for topical application. In particular, the present invention relates to pharmaceutical compositions for topical application in the form of a gel comprising a non-steroidal anti-inflammatory drug and a xanthine derivative. The compositions of the present invention are useful as analgesics and anti-inflammatories.

Background of the Invention

Xanthine derivatives are known for use in pharmaceutical compositions. Caffeine is a particularly well known xanthine derivative. Caffeine, or 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione, has the structural formula:



Caffeine has been used alone, intravenously, in the treatment of headaches and has also been used in combination with selected drugs. One of the types of topical formulations that caffeine has been used in is a topical gel. A commercial aqueous gel product containing caffeine for topical treatment of skin is Percutafeine gel, supplied by Laboratories Pierre Fabre Sante, Paris, France, which contains 4% by weight of caffeine and which is used to treat obesity. EP-A-0105635 (Han & Roehrs, published 18 April 1984) relates to ophthalmic aqueous gel compositions for reducing ocular stinging comprising an acidic anti-inflammatory agent and a xanthine derivative.

Ibuprofen (i.e. 2-(4-isobutylphenol) propionic acid) is well known non-steroidal anti-inflammatory drug for use in oral compositions as a

therapeutic agent having analgesic, anti-inflammatory and anti-pyretic activity. It is often used as an alternative to aspirin (i.e. acetyl salicylic acid) and paracetamol, in the treatment of pain such as headache, toothache and especially when associated with inflammation in, for example, rheumatic diseases. Ibuprofen is also known for use in aqueous gel compositions for topical application to the skin.

The combination of ibuprofen and xanthine derivatives is known in the art for use in pharmaceutical compositions. GB-A-2134786 (Sunshine, published 8 May 1986) discloses oral pharmaceutical compositions comprising a non-steroidal anti-inflammatory drug (NSAID) analgesic, anti-inflammatory drug active such as ibuprofen, together with caffeine. EP-A-0105635 discloses ophthalmic compositions which may be aqueous solutions, suspensions or gels comprising an acidic anti-inflammatory agent, such as ketoprofen, and a xanthine derivative, such as caffeine. There are no examples in this document of aqueous gel compositions containing a xanthine derivative and a non-steroidal anti-inflammatory drug.

It would be desirable to provide an aqueous gel composition for topical application to the skin comprising a combination of a xanthine derivative such as caffeine and non-steroidal analgesic/anti-inflammatory drug such as ibuprofen, which delivers analgesic or anti-inflammatory efficacy. However, since both ibuprofen and caffeine-type drugs are water-insoluble or have very low solubility in water, it is difficult to formulate aqueous gel compositions containing both of them which are stable and clear.

It is therefore an object of the present invention to provide aqueous gel formulations containing a non-steroidal anti-inflammatory drug and a xanthine derivative having improved product stability and clarity.

It is a further object of the present invention to provide aqueous gel formulations containing a non-steroidal anti-inflammatory drug and a xanthine derivative which is clear.

It is a further object of the present invention to provide an aqueous gel formulation containing a non-steroidal anti-inflammatory drug and a xanthine derivative which exhibits the benefits achievable by such combination of active ingredients.

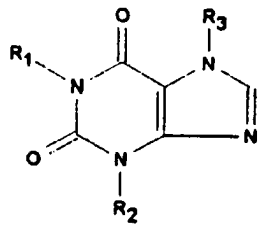
These and other objects and benefits of the invention as may become apparent or known to those skilled in the art upon reading this patent can be obtained in accordance with the invention described below.

Summary of the Invention

Hence according to the present invention there is provided a topical gel composition comprising:

(a) from about 0.1% to about 10% by weight of a non-steroidal anti-inflammatory drug selected from a propionic acid derivative, acetic acid derivative, fenamic acid derivative, biphenylcarboxylic acid derivative and an oxicam, and salts thereof, and mixtures thereof;

(b) from about 0.1% to about 10% by weight of xanthine derivative having the general formula:



wherein R1, R2 and R3 are each independently selected from a hydrogen atom, a methyl or ethyl group, and at least two of R1, R2 and R3 are methyl or ethyl groups; and mixtures thereof;

(c) from about 0.5% to about 10% by weight of gelling agent;

(d) from about 5% to about 60% by weight of cosolvent for said non-steroidal anti-inflammatory drug and said xanthine derivative; and

(e) from about 10% to about 90% by weight of water.

The compositions of the present invention exhibit analgesic and anti-inflammatory activity and improved product stability and clarity.

All weights and ratios herein are by weight unless otherwise specified. All weight percentages are by weight of the total composition unless otherwise specified.

Detailed Description of the Invention

In general, the compositions of the present invention comprise a non-steroidal anti-inflammatory drug, a xanthine derivative, a gelling agent, a cosolvent for the non-steroidal anti-inflammatory agent and the xanthine derivative and water.

The compositions of the present invention are gels which have improved clarity and stability. Preferably the compositions are formulated as clear gels. As used herein in relation to gels the term "clear" is intended to have an ordinary dictionary meaning, that is, transparent and free from obscurity. Product clarity can be measured using a visible range spectrophotometer. Using this equipment the percent transmittance of the sample at 450 nm is measured by calibration against a reference sample of Ethanol B100 as 100% transmittance. Percent transmittance values for the gel compositions according to the present invention are preferably greater than 70% when first made, preferred compositions herein displaying 80% transmittance values after storage for at least four weeks at 37°C.

A first essential component of the compositions herein is a non-steroidal anti-inflammatory agent selected from a propionic acid derivative, an acetic acid derivative, a fenamic derivative, a biphenylcarboxylic acid derivative and an oxicam derivative, and salts

thereof, and mixtures thereof. The term "non-steroidal anti-inflammatory agent" as used herein is intended to mean any non-narcotic analgesic non-steroidal anti-inflammatory compound, including the pharmaceutically acceptable non-toxic salts thereof, falling within one of the five structural categories above.

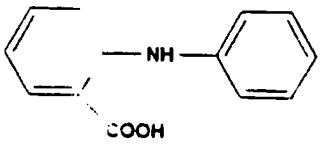
The term "propionic acid derivative" as defined herein means non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-CH(CH_3)COOH$ or $-CH_2CH_2COOH$ group or a combination thereof (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g. $-CH(CH_3)COO^-Na^+$ or $-CH_2CH_2COO^-Na^+$), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

Suitable propionic acid derivatives for use herein include, but are not limited to, ibuprofen, naproxen, benoxaprofen, flurbiprofen, indoprofen, fenoprofen, ketoprofen, fenbufen and fluprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid and bucloxic acid. Structurally related propionic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. It will be appreciated by those skilled in the art that any of the foregoing compounds may be utilized in the form of their pharmaceutically-acceptable salt forms, e.g., sodium salts, potassium salts, and the like, and such salts are intended to be included. Particularly preferred propionic derivatives for use herein include ibuprofen, naproxen, naproxen sodium, flurbiprofen, fenoprofen, ketoprofen, suprofen, fenbufen and fluprofen, especially ibuprofen.

The term "acetic acid derivatives" as used herein means non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-CH_2COOH$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g. $-CH_2COO^-Na^+$), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system. Examples of suitable acetic acid derivatives for use herein include, but are not limited to, indomethacin, sulindac, tolmetin, diclofenac, fenclofenac, alclofenac, ibufenac,

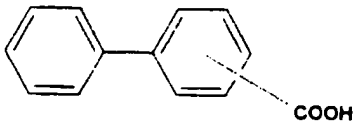
isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac and oxepinac. Structurally related acetic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

The term "fenamic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:



which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g. $-COO^-Na^+$. The fenamic acid derivatives suitable for use herein include, but are not limited to, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid and tolfenamic acid. Structurally realted fenamic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Representative members of the fenamic group include mefenamic acid, meclofenamate sodium (meclofenamic acid, sodium salt) and flufenamic acid.

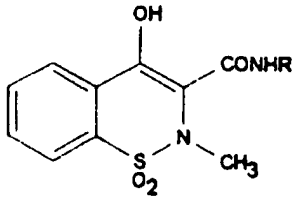
The term "biphenylcarboxylic acid derivatives" as used herein means non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:



which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g. $-COO^-Na^+$. Suitable biphenylcarboxylic acid derivatives for use herein include, but are not limited to, diflunisal and flufenisal. Structurally realted biphenylcarboxylic acid derivtiaves having simipar

analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

The term "oxicams" as defined herein means non-narcotic analgesics/non-steroidal anti-inflammatory drugs which have the general formula:

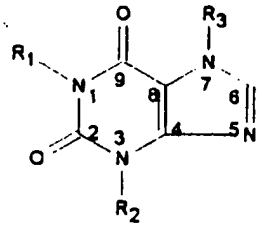


wherein R is an aryl or heteroaryl ring system. Suitable oxicams for use herein include, but are not limited to, piroxicam, sudoxicam, and isoxicam. Structurally related oxicams having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Of the foregoing non-steroidal anti-inflammatory drugs, the propionic acid derivatives are most preferred for use in the compositions herein, and especially ibuprofen.

The non-steroidal anti-inflammatory agent is present in the compositions of the present invention at a level of from about 0.1% to about 20%, preferably from about 0.1% to about 15%, especially from about 1% to about 10% by weight of composition.

A second essential component of the compositions of the present invention is a xanthine derivative having the general formula:



wherein R_1, R_2 and R_3 are each independently selected from a hydrogen atom, a methyl or ethyl group, and at least two of R_1, R_2 and R_3 are methyl or ethyl groups, and mixtures thereof.

The xanthine derivative is generally present herein at a level of from about 0.1% to about 10%, especially from about 1% to about 5% by weight of composition. Particularly preferred for use herein are methyl and ethyl derivatives of xanthine. Examples of xanthine derivatives include theophylline, which has methyl groups at the 1 and 3 positions, caffeine, which has methyl groups at the 1,3, and 7 positions, and theobromine which has methyl groups at the 3 and 7 positions. Preferred herein in combination with the non-steroidal anti-inflammatory drug from the viewpoint of enhancing analgesic and/or anti-inflammatory activity is caffeine.

A third essential ingredient herein is a gelling agent for forming a gel in the aqueous base of the compositions of the present invention. The gelling agent is generally present in the compositions herein at a level of from about 0.1% to about 10%, preferably from about 0.5% to about 5%, more preferably from about 0.5% to about 3% by weight.

Suitable gelling agents for use herein include crosslinked polymeric gelling agents. These can be obtained by the polymerisation or copolymerisation of appropriate monomers together with a suitable crosslinking agent.

Suitable monomers for use in the crosslinked polymeric gelling agents include unsaturated, polymerizable carboxyl-containing monomers. Monomers for use herein can be monoethyleneically or polyethyleneically unsaturated. Suitable monomers of this type include acrylic acid, methacrylic acid, ethacrylic acid, beta-methacrylic acid (crotonic acid), cis-alpha-methylcrotonic acid (angelic acid), trans-alkpha-methyl-crotonic acid (tiplic acid), alpha-butylcrotonic acid, alpha-phenylacrylic acid, alpha-benzylacrylic acid, alpha-cyclohexylacrylic acid, beta-phenylacrylic acid (cinnamic acid), coumaric acid (ortho-hydrocinnamic acid), umbellic acid (p-

hydroxycoumaric acid) and the like. Mixtures of these monomers can also be used.

Preferred monomers for use herein are carboxyl-containing monoethyleneically unsaturated monomers, especially acrylic acid.

Copolymers prepared from one or more of the above monomers together with one or more other monomers can also be used as long as the resulting copolymers are safe and effective for use as gelling agents in the compositions herein.

Suitable crosslinking agents for use herein include non-polyalkenyl polyether difuntional crosslinking monomers, polyalkenyl polyether crosslinking agents and diolefinic non-hydrophilic macromeric crosslinking agents.

Suitable non-polyalkenyl polyether difunctional crosslinking agents include divinyl glycol, 2,3-dihydroxyhexa-1,5,-diene, 2,5-dimethyl-1,5-hexadiene, divinylbenzene, N,N-diallylacrylamide, N,N-diallylmethacrylamide and the like. Suitable polyalkenyl polyether crosslinking agents include those containing two or more alkenyl ether groupings having terminal $H2C=C<$ groups, prepared by etherifying a polyhydric alcohol containing at least four carbon atoms and at least three hydroxyl groups with an alkenyl halide such as allyl bromide or the like, e.g. polyallyl sucrose, polyallyl pentaerythritol, or the like. Suitable diolefinic non-hydrophilic macromeric crosslinking agents include those having molecular weights of from about 400 to about 8,000 such as insoluble di- and polyacrylates and methacrylates of diols and polyols, diisocyanate-hydroxyalkyl acrylate or methacrylate reaction products, and reaction products of isocyanate terminated prepolymers derived from polyester diols, polyether diols or polysiloxane diols with hydroxyalkylmethacrylates, and the like.

The crosslinking agent is generally present at a level in the range of from about 0.05% to about 5%, preferably from about 0.1% to about 5%, especially from about 0.75% to about 2% by weight of the polymer.

Preferred gelling agents for use herein are polyalkenyl polyether-crosslinked polymers of carboxyl-containing monethyleneically unsaturated monomers. More preferred gelling agents for use herein are polyalkenyl polyether-crosslinked polymers of acrylic acid. Especially preferred gelling agents for use herein are polyallyl sucrose or polyallyl pentaerythritol-crosslinked polymers of acrylic acid. Examples of such polymers include those commercially available under the tradename Carbopol, such as Carbopol 934, 934P, 940, 941, 974P, 980, 981, manufactured by B.F.Goodrich Chemical Company, U.S.A. A preferred gelling agent for use herein is Carbopol 980 which is a polyallylsucrose-crosslinked polymer of acrylic acid.

Also suitable for use herein are hydrophobically-modified carboxylate monomers, such as C1-C30 alkyl substituted carboxylate-containing monomers, such as C1-C30 acrylic acid (acrylate) monomers. These can be used to form hydrophobically modified, cross-linked copolymers wherein the modified polymeres have amphipathic properties. Examples include copolymers of acrylic acid and C1-C30 alkyl substituted acrylic acid, such as those available under the Trade Name Carbopol 1342 and Pemulen TR-1 (CTFA Designation: Acrylates/10-30 Alkyl Acrylate Crosspolymer). Combinations of the polyalkenyl polyether cross-linked acrylic acid polymer and the hydrophobically modified cross-linked acrylic acid polymer are also suitable for use herein.

It is preferable to neutralize the acidic group-containing hydrophilic gelling agents. Neutralizing agents suitable for use herein include sodium hydroxide, potassium hydroxide, ammonium hydroxide, monoethanolamine, diethylamine, diisopropanolamine, diethanolamine and triethanolamine. A preferred neutralizing agent for use herein is diethylamine. The neutralizing agent is preferably present in a level from about 0.1% to about 5%, preferably from about 2% to about 5% by weight.

Other suitable gelling agents for use herein are lower alkyl ethers of cellulose. The lower alkyl ether of cellulose suitable for use herein

results fom at least partial substitution of the same or different lower alkyl ether groups for a plurality of hydroxyl groups of cellulose. The lower alkyl ether groups may be substituted by substituents. Preferred examples of such substituents are a hydroxyl group, and alkali metal carboxylate groups such as sodium carboxylate group.

Examples of the optionally substitued lower alkyl groups are a methyl group, hydroxy lower alkyl groups having 2 or 3 carbon atoms, and carboxylate groups resulting from substitution of an alkali metal for the hydrogen atom of the carboxyl group of a carboxy lower alkyl group having 2 or 3 carbon atoms. Specific examples of the hydroxy lower alkyl groups are B-hydroxyethyl and B-hydroxypropyl groups, and specific examples of the carboxylate groups are carboxylate groups resulting from substitution of an alkali metal for a carboxymethyl, a-carboxyethyl or B-carboxyethyl group.

Specific examples of the lower alkyl ethers of cellulose include methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethylhydroxyethyl cellulose, and sodium carboxymethyl cellulose. Preferred cellulose ethers for use herein are methyl cellulose, hydroxypropyl cellulose and hydroxypropylmethyl cellulose.

The lower alkyl ethers of cellulose can be used either singly or in combination with each other, or with other gelling agents.

Preferably the gelling agent used herein has a viscosity (Brookfield RVT, Spindle No. 7, 20 rpm, 20°C, undiluted) of at least about 4,000 mPa.s, preferably at least about 10,000 mPa.s. Preferred gelling agents for use herein have an average molecular weight in the range from about 1,000,000 to about 4,500,000.

A fourth essential component of the compositions herein is a cosolvent for the xanthine derivative and the non-steroidal anti-inflammatory drug. Suitable cosolvents for use herein include any solvent which is miscible with water and which is suitable for topical application which aids in the solubilisation of the xanthine derivative and the non-

steroidal anti-inflammatory drug. Suitable cosolvents include straight chain and branched chain alcohols having from 1 to 6 carbon atoms, and mixtures thereof. The preferred cosolvent for use herein is a straight chain alcohol having from 1 to 4 carbon atoms, especially ethanol.

The solvent is generally present herein in a level of from about 5% to about 60% by weight.

The compositions herein also comprise water, generally from about 10% to about 90%, preferably from about 30% to about 80%, more preferably from about 30% to about 60% by weight of water.

The gel compositions preferably have a pH of from about 3 to about 8, more preferably from about 4 to about 7, more preferably about 7, and a viscosity of from about 10,000 to about 50,000, preferably from about 20,000 to about 40,000 cps (Brookfield RVT, 20°C, Spindle 7, 20 rpm, undiluted)

The compositions herein can comprise a wide range of optional ingredients.

A surfactant can be present in the compositions herein. Suitable surfactants for use herein include anionic, nonionic, cationic, amphoteric and zwitterionic surfactants and mixtures thereof. When present the surfactant is preferably at a level of up to about 1% by weight of composition.

The compositions herein can contain cooling agents such as menthol. Preferably, menthol is present in the compositions herein, when used, at a level of from about 0.1% to about 5%, preferably from about 1% to about 5% by weight.

The compositions herein can additionally include preservatives. These can be water-soluble or solubilizable preservatives such as DMDM Hydantoin (RTM), Germall (RTM) 115, methyl, ethyl, propyl and butyl esters of hydrobenzoic acid, benzoic acid, Euxyl (RTM) K400,

Bronopol (RTM) (2-bromo-2-nitropropane-1,3-diol), sodium benzoate, chlorhexadine, benzalkonium chlorides and 2-phenoxyethanol, Cetrimide, potassium sorbate and thiomersal. Preferred preservatives for inclusion in the present invention are methyl and propyl parabens. In general, amounts of from about 0.005% to about 0.5% are suitable herein with amounts of from about 0.01% to about 0.1% being preferred.

The compositions of the invention may comprise additional therapeutic agents including steroids, antibiotics, antiinfectives and antiallergics such as antihistamines, and other ingredients for modifying the appearance or aesthetic propertise of the composition, such as fragrances, colouring agents, and the like.

The following examples illustrate the compositions of the present invention.

Examples I-V

	I/%	II/%	III/%	IV/%	V/%
Carbopol 980[1]	2	3	2	3	2
Caffeine	4	4	4	3	3.8
Propylene Glycol	14.5	14.5	14.5	14.5	13.5
Ethanol	25	5	25	30	23
Ibuprofen 38[2]	5	5	5	5.5	4
Diethylamine	3	3.25	3	3	3.5
Menthol	0	3	0	0	0
Methyl Salicylate	0	0	3	0	0
Water	----------to 100----------				

1. Commercially available from B.F. Goodrich, PO Box 527, Calvart City, NY 42029, USA
2. Commercially available from Boots, Thame Road, Nottingham, UK

The compositions can be prepared as follows. The Carbopol is dissolved in water with stirring and then the caffeine is added, followed by addition of propylene glycol. Separately, the ibuprofen is dissolved

in the ethanol and the resulting premix is added to the main batch. The diethylamine is finally added quickly to produce the required gel.

When methyl salicylate is part of the final composition it is added to the ethanol before the ibuprofen. When menthol is part of the final composition, menthol is dissolved in a small amount of ethanol before being added to the main batch. In addition, the caffeine is added to the main batch just before the diethylamine.

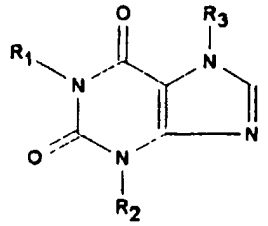
The compositions of the examples exhibit excellent product stability and clarity and excellent analgesic and anti-inflammatory activity when applied to the skin.

What is claimed is:

1. Topical gel composition comprising:

(a) from about 0.1% to about 20% by weight of a non-steroidal anti-inflammatory drug selected from a propionic acid derivative acetic acid derivative, fenamic acid derivative, biphenylcarboxylic acid derivative and an oxicam, and salts thereof, and mixtures thereof;

(b) from about 0.1% to about 10% by weight of xanthine derivative having the general formula:



wherein R1, R2 and R3 are each independently selected from a hydrogen atom, a methyl or ethyl group, and at least two of R1, R2 and R3 are methyl or ethyl groups, or mixtures thereof;

(c) from about 0.5% to about 10% by weight of gelling agent;

(d) from about 5% to about 60% by weight of cosolvent for said non-steroidal anti-inflammatory drug and said xanthine derivative;

(e) from about 10% to about 90% by weight of water.

2. A composition according to Claim 1 wherein the composition is clear.

3. A composition according to Claim 1 or 2 wherein said propionic acid derivative is selected from ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenprofen,

ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, trioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen or bucloxic acid, and salts thereof and mixtures thereof.

4. A composition according to Claim 1 or 2 wherein said acetic acid derivative is selected from indomethacin, sulindac, tolmetic, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxepinac, and salts thereof, and mixtures thereof.

5. A composition according to Claim 1 or 2 wherein said fenamic acid derivative is selected from mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, and salts thereof, and mixtures thereof.

6. A composition according to Claim 1 or 2 wherein said biphenylcarboxylic acid is selected from diflunisal and flufenisal, and salts thereof, and mixtures thereof.

7. A composition according to Claim 1 or 2 wherein said oxicam comprises piroxicam, sudoxicam and isoxicam, and salts thereof, and mixtures thereof.

8. A composition according to Claim 1 or 2 wherein the non-steroidal anti-inflammatory drug is a propionic acid derivative.

9. A composition according to Claim 8 wherein the propionic acid derivatives is ibuprofen.

10. A composition according to any of Claims 1 to 9 wherein the xanthine derivative is selected from theophylline, caffeine, theobromine or a mixture thereof.

11. A composition according to any of Claims 1 to 10 wherein the xanthine derivative is caffeine.

12. A composition according to any of Claims 1 to 11 wherein the gelling agent has a viscosity (undiluted, 20°C, Brookfield RVT Spindle 6, 20 rpm) of at least about 4,000 mPa.s, preferably at least about 10,000 mPa.s.

13. A composition according to any of Claims 1 to 12 wherein the gelling agent comprises a carboxyvinyl polymer, preferably a colloidally water-soluble polymer of acrylic acid cross-linked with from about 0.05% to about 5% of a cross linking agent selected from polyallyl sucrose and polyallyl pentaerythritol.

14. A composition according to any of Claim 1 to 13 wherein the gelling agent comprises a hydrophobically modified cross-linked polymer of acrylic acid having amphipathic properties.

15. A composition according to any of Claims 1 to 14 wherein the cosolvent is selected from straight or branched chain alcohols having from 1 to 6 carbon atoms, preferably ethanol.

16. A composition according to any of Claims 1 to 15 comprising from about 0.1% to about 15%, preferably from about 1% to about 10% by weight of the non-steroidal anti-inflammatory drug.

17. A composition according to any of Claims 1 to 16 comprising from about 0.1% to about 25%, preferably from about 1% to about 5% by weight of the xanthine derivative.

18. A composition according to any of Claims 1 to 17 comprising from about 0.1% to about 10%, preferably from about 0.5% to about 5%, more preferably from about 0.5% to about 3% by weight of gelling agent.

19. A composition according to any of Claims 1 to 18 comprising from about 5% to about 30% by weight of the cosolvent.

20. A composition according to any of Claims 1 to 19 additionally comprising from about 0.1% to about 25% by weight of methyl salicylate.

21. A composition according to any of Claims 1 to 20 additionally comprising from about 0.1% to about 20% by weight of menthol.

22. Use of from about 0.1% to about 10% by weight of ibuprofen and from about 0.1% to about 10% by weight of caffeine for the manufacture of a medicament in the form of a topical aqueous gel suitable for topical application for the treatment of inflammatory diseases.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/11205

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/52 A61K31/54 //(A61K31/52,31:19),(A61K31/52,31:195), (A61K31/54,31:52)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 105 635 A (ALCON LAB INC) 18 April 1984 cited in the application * claims 1-10, especially claims 1 and 9 * ---	1-22
P,Y	WO 96 30022 A (ALCON LAB INC) 3 October 1996 * p.4; p.5, l.1-4; claims 4-12 * -----	1-22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
12 November 1997	26. 11. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Uiber, P

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/11205

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